IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	9096
Serial No.:	09/838,286	Examiner:	KWON, Brian Yong S.
Filed:	April 20, 2001	Group Art Unit:	1614

Title: HETEROARYL UREAS CONTAINING NITROGEN HETERO-ATOMS AS P38 KINASE INHIBITORS

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to: Commissioner of Patents, P O Box 1450, Alexandria, VA 22313-1450 on: May 1, 2006
Name: Richard J. Traverso
Signature: [signature]

Sir:

Further to the Notice of Appeal filed on October 31, 2005, please consider the following.

The attached check includes the fee of $500.00 as set forth under § 41.20(b)(2) and the fee of $1,590.00 for a four-month extension of the period to respond . The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is: BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane, West Haven, Connecticut 06516, United States of America, a corporation organized under the laws of the State of Delaware, United States of America.

(ii) RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences on subject matter directly related to this application.

(iii) STATUS OF CLAIMS

Claims 26 and 39-74 are pending in the present application.

Claims 26, 39-49, 51 and 57-74 are withdrawn from consideration following an election of species requirement.

Claims 50 and 52-56 are rejected and are on appeal. These claims appear in the attached Appendix.

(iv) STATUS OF AMENDMENTS

No amendments were filed or proposed after the final rejection.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to methods for treating a disease mediated by the enzyme p38 within a host by administering a diaryl urea of Formula I: A-D-B (I); or a pharmaceutically acceptable salt thereof. (See page 7, line 29 to page 8, line 1.) The entity D represents a urea moiety (see page 8, line 5) and entity A is a specific heteroaryl moiety selected from t-butylpyridinyl, (trifluoromethyl) pyridyl, isoquinolinyl or quinolinyl, which can be substituted or unsubstituted (see page 8, line 6; page 13, line 28-30 and page 14, lines 2-3). Entity B is selected from a group of substituted or unsubstituted aryl moieties, hetaryl moieties or is a bridged cyclic structure of the formula –L $(ML^1)_q$, wherein q is an integer of 1-3, L^1 and L are each independently selected from a group of aryl or hetaryl moieties and M is bridging group such as –O-, -CH_2- and -S-. (See page 8, lines 10-20, page 13, lines 3-7, and page 13, lines 14-17.) The substituents for these moieties are defined in claims 50 and 52-53. (see page 10, lines 24-28, page 14, lines 29-30, page 11, lines 1-2, and page 13, lines 18-20). Claim 54 is directed to salt forms of the compounds of formula I (see page 17, lines 6-21). The treatment of diseases other than cancer are preferred and preferred methods treat the diseases recited in claim 56 and on pages 6 and 7 of the specification, such as rheumatoid arthritis, osteoarthritis, septic arthritis, and corneal ulceration.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejection to be reviewed are:

(1) the rejection under 35 U.S.C. § 112, first paragraph, i.e., whether claims 50, 52-55 directed to methods for the treatment of diseases mediated by p38 within a host are enabled.

(vii) ARGUMENT

Method claims 50, 52-55 are directed to treating diseases "mediated by p38" using the compounds of formula I. The functional definition used to define the diseases is commensurate in scope with the p38 kinase activity of the compounds of formula I, which is demonstrated by the results (IC_{50} values) of the in-vitro p38 kinase assay disclosed in the specification on page 74 and confirmed by the in-vivo p38 kinase assay disclosed on page 75 of the specification.

Method claim 55 further defines the diseases to be treated as "other than cancer," and therefore, claims a narrower scope of diseases to be treated.

The specification cites a number of publications on pages 2-5, which are representative of the state of the art at the time of the invention. These publications have correlated TNF production and MMP production with a number of diseases. Since inhibition of p38 leads to the inhibition of TNF and MMP production, the p38 inhibitors of this invention will be useful in treating these diseases. No evidence has been presented to refute the findings or conclusions made in these publications or the present application. No evidence has been presented that any compounds of this invention, as inhibitors of p38, would not be effective in treating the diseases defined by this functional language. Furthermore, no evidence has been presented of the "undue experimentation " allegedly necessary to practice the invention commensurate in scope with the claims.

Only unsupported allegations and conclusions regarding the state of the art are provided to support the rejection such as, "There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated through p38 or (ii) all types of diseases other than cancer that are mediated by p38." Appellants wish to draw attention to US Patent No. 5,932,576, which contains claims to treating p38 mediated diseases using other small molecule compounds. The inventors of the '576 patent disclose the ability of the named compounds to inhibit p38 through in-vitro and in-vivo assays, as do the Appellants in their

application. Others have defined the treatment of numerous inflammatory diseases using functional language similar to that used here. For example, US Pat. Nos.5,593,991 and 5,593,992 claim the treatment of "cytokine mediated diseases," with small molecules, the activity of which is demonstrated by in-vitro assays. Therefore, contrary to the Examiner's allegation, those skilled in the art have recognized and claimed that certain compounds can be effective for treating all types of diseases mediated by p38.

Even if these allegations regarding the prior art were true, they are not relevant to the issue of enablement. As discussed in Wands, cited by the Examiner, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." No evidence has been presented that the specification is deficient in this regard. Again, only unsupported allegations are made that undue experimentation is necessary to practice the invention.

It is alleged that the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and sequentially administering the instant compounds. Certainly the step of administering the instant compounds does not require undue experimentation and the large number of diseases already correlated with TNFα production and MMP production (1) do not require undue experimentation to be identified y and (2) suggest identifying new disorders mediated by p38 does not require undue experimentation.

To support the argument that undue experimentation is needed to practice the claimed invention, the examiner cites In re Buting, 163 USPQ 689 (CCPA 1969), for the principal that evidence involving a single compound is insufficient to establish the utility of claims to disparate types of cancers. The state of the art of cancer treatment has advanced significantly in 35 years and, as shown by the citations on pages 3-5 of the specification, there is evidence suggesting these compounds will be effective in treating more than one disease. While the various types of diseases are seemingly unrelated , they are linked in that they are all mediated by p38.

The examiner has not found the links of p38 to a number of disorders to be sufficient evidence to support the claim. The examiner is requiring that the application meet clinical

standards as set by the FDA to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph in stating , "there is no proof or any competent evidence provided in the state [of the] art that inhibition of p38 leads to effective treatment of the claimed disease conditions." The proof required by the Examiner requires a showing of efficacy and safety, which is beyond what is necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. An applicant is not required to test the claimed compounds in their final use (rigorous planned and executed clinical trials..." per the Examiner) to satisfy the enablement requirement of 35 USC §112, first paragraph. As stated in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs will prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures in any crucial area such as the treatment of cancer.

Although directed to the issue of utility, this rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

It is alleged that appellants have not identified any state of the art references that clearly establish correlation between the assays employed in the specification and clinical efficacy for the treatment of the claimed diseases. Such a showing is not necessary here. The specification provides an objectively enabling disclosure and there is no necessity for any assay data at all. In any event, the party in interest is a pharmaceutical manufacturer, which would only use assays that were reasonably correlated with efficacy to find new products.

In any event, the specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of the diseases identified (see pages 22-26). The specification also provides dosage ranges for the various methods of administration (see

pages 26-27). In fact, the specification provides more than it needs to, e.g., *in vitro* p38 kinase assays (and IC_{50} data) and *in vivo* assays. In similar fashion, one of ordinary skill in the art, by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various diseases. This is absolutely routine in the field. Thus, appellants have provided more than adequate guidance (and examples) to enable the claimed invention. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited diseases with a compound of this invention.

Even absent the specification disclosures discussed above, the rejection is clearly deficient in general under controlling case law. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those of ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the claimed invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Using the claimed compounds would be routine for those of ordinary skill in the art in view of applicant's disclosure. "An inventor need not ... explain every detail since he is speaking to those skilled in the art," *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be," *In re Gay*, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962).

There is no requirement that an applicant provide any working examples relating to the treatment of every claimed disease to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art");

Utter v Higara, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, as discussed earlier, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make and use the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and conclusions. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds without undue experimentation.

No evidence has been presented that any compounds of this invention, as inhibitors of p38 kinase, would not be effective in treating the conditions identified. Only unsupported allegations and conclusions regarding the art are provided to support the rejection. Furthermore, there is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). Applicants here provided a detailed disclosure and examples of how to make and use the claimed compounds in the methods claimed. The statute (35 USC 112) does not require more.

Double Patenting and Priority Claim

The provisional obviousness type double patenting rejection is not ripe for appeal . Many of the claims in US application No. 10/361,858, upon which the rejection is based, have been cancelled. Similarly, no rejection has been raised wherein the priority claim is relevant.

(viii) Conclusion

For the reasons stated above, Appellants respectfully submit the subject matter of the claims on appeal satisfy the requirements of 35 U.S.C. §112, first paragraph. Therefore, Appellants respectfully request the outstanding rejection be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402

Respectfully submitted,

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(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None

(xi) APPENDIX OF CLAIMS ON APPEAL

50. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a

substituted t-butylpyridinyl, unsubstituted t-butylpyridinyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl, substituted quinolinyl or unsubstituted quinolinyl, and

B is a substituted or unsubstituted, phenyl naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl or a bridged cyclic structure of the formula $-L(ML^1)_q$, wherein q is an integer of 1-3, and L^1 and L are each independently thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl substituted quinolinyl, isoquinolinyl or substituted isoquinolinyl and M is –O-, $-CH_2-$, -S-, -NH-, -C(O)-, $-O-CH_2-$or $-CH_2-O-$, with cyclic structure L bound directly to D,

wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3 and each W is independently selected from the group consisting of

C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O; C_{2-10} alkenyl, C_{1-10} alkenoyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S, C_4-C_{24} alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6-C_{14} aryl, substituted C_7-C_{24} alkaryl,

substituted C_7-C_{24} aralkyl, substituted C_3-C_{12} heteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S, substituted C_4-C_{24} alkheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

-CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl, C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_6-C_{14} aryl and up to per halo substituted C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, and $-NR^7C(O)R^{7'}$, wherein R^7 and $R^{7'}$ are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J_n, where n is 0-3 and each J is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently as defined for W above, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-14} aryl, C_{3-12} hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6 - C_{14} aryl, substituted C_{3-12} hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl, substituted C_7-C_{24} aralkyl and substituted C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S,

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^{7'}$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^{7'}$, $-NR^7C(O)R^{7'}$, and $-NR^7C(O)OR^{7'}$, with R^7 and $R^{7'}$ as defined above for W.

52. A method of claim 50, wherein A has 1-3 substituents selected from the group consisting of C_{1-10} alkyl, up to per halo substituted C_{1-10} alkyl, -CN, -OH, halogen, C_{1-10} alkoxy, up to per halo substituted C_{1-10} alkoxy and C_{3-10} heterocyclic moieties having at least 5 cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur.

53. A method of claim 50 wherein L^1 is substituted 1 to 3 times by one or more substituents selected from the group consisting of -CN, halogen up to per halo, C_{1-10} alkyl, C_{1-10} alkoxy,-OH, up to per halo substituted C_{1-10} alkyl, up to per halo substituted C_{1-10} alkoxy, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$ $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)R^7$ or $-NO_2$, wherein each R^7 and $R^{7'}$ is independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl.

54. A method of claim 50 wherein a pharmaceutically acceptable salt of a compound of formula I is administered which is selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

55. A method as in claim 50 for the treatment of a disease other than cancer.

56. A method as in claim 50 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system.